

respectfully submit that claims 11-13 read on the elected species. The Examiner is directed to the contrast agent of Example 7, where the second composition as required by item (ii) of claim 1 is the product described in Preparation 9. The diffusible component here is perfluoromethylcyclopentane, which is listed as a species in claim 13 as well as being included more generically in claim 11 (perfluorocarbon) and claim 12 (perfluorocycloalkane). As claims 11-13 therefore read on the elected species, Applicants respectfully request their re-entry into the instant application.

Claims 1-10 and 14 are rejected under the judicially-created doctrine of obviousness-type double patenting over claims 1-3, 5-10, 12-14 and 18 of United States Patent No. 6,735,931. This rejection is respectfully traversed.

The present invention claims a contrast agent preparation having a first and second composition. The first composition includes a dispersed gas and the second composition includes an oil phase. The material present at the surface of the dispersed gas and the oil phases have opposite charges so as to have an affinity for each other.

The advantages of products which incorporate this feature are discussed at page 5 line 23 *et seq.* of the parent PCT specification. In particular, by designing the dispersed gas and the dispersed diffusible component to have electrostatic affinity for each other, the probability of interaction between them is greatly increased, particularly during ultrasound-induced activation. Contrast agents according to the instant invention may therefore be used at significantly lower doses than are suggested in the '931 patent, while

still giving equivalent contrast effects. There are consequential benefits with regard to product safety and toxicity considerations.

This behavior is confirmed by Examples 1 and 2 of the present specification, in which comparisons are made between preparations of the present invention and preparations in which the two component compositions have the same surface charge. Example 1(a) is a comparative test illustrating imaging using a product in which both compositions (i) and (ii) utilise negatively charged stabilisers. Examples 1(b) and 1(c) use products in which composition (i) incorporates a negatively charged stabiliser and composition (ii) incorporates a positively charged stabiliser. In Example 1(b) the dose of the diffusible component in composition (ii) is reduced fourfold compared to Example 1(a), but far more intense and longer lasting myocardial contrast effect is observed. In Example 1(c) the dose of the diffusible component is reduced tenfold compared to Example 1(a), but comparable myocardial contrast is still observed. Similar results are shown in Example 2(a) and 2(d), whereas Examples 2(b) and 2(c) show that only faint myocardial effects could be observed at these low diffusible component doses where there is no charge interaction between the stabilising surface materials of the two compositions.

Therefore, as the '931 patent fails to disclose, teach, or suggest the two compositions of a contrast agent having electrostatic affinity, as is claimed by the present invention, Applicants respectfully submit that the present invention is patentably distinct thereover. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1-10 and 14-17 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Unger et al. (WO 97/40858) and Lohrmann (United States Patent No. 5,716,597). This rejection is respectfully traversed.

It is accepted that Unger teaches fluorinated gas-filled microspheres which incorporate lipid stabilisers and which may be used as potential ultrasound contrast agents. It is also correct that Unger describes the use of negatively charged lipids to enhance stability, although it is important to note that such negative lipids are used in only "a small amount" relative to the total lipid content (see page 15 lines 18-22).

It is likewise accepted that Lohrmann described oil-in-water emulsions potentially of use as ultrasound contrast agents. The disclosure suggests that the dispersed oil phase may be converted to echogenic gas microbubbles following activation by exposure to ultrasonic energy.

The Examiner states that "it would have been obvious to one of ordinary skill in art at the time the invention was made to combine the teachings of Unger and Lohrmann and arrive at a single combination contrast agent". It is respectfully submitted that, regardless of whether or not this is so, such a combination of references would not suggest the features of instant claim 1 or any of the claims dependent thereon.

A first key feature of the instant invention is that the diffusible component present as the oil phase in composition (ii) is capable of diffusion *in vivo* into the dispersed gas of

composition (i) so as to increase the size of this dispersed gas. Such growth of the gas phase *in vivo* permits controllable and temporary retention of the gas phase, for example in the form of microbubbles, in tissue microvasculature, thereby enhancing the concentration of echogenic gas in such tissue, for example relative to the blood pool.

Such controllable use of gas as a temporary deposited perfusion tracer is a new concept which runs contrary to previous thinking in the art that growth of dispersed gas microbubbles *in vivo* should invariably be avoided on the basis that uncontrolled growth may lead to potentially hazardous tissue embolisation.

The contrast agents of the invention therefore exhibit a number of major advantages over prior art ultrasound contrast agents. Thus for example, echogenicity of tissue in which gas is temporarily retained in the microvasculature will be enhanced relative to the blood pool (see page 2 lines 3-6 of the specification). Temporary retention of gas may be directed to a particular target organ within a subject, for example by using preliminary localised ultrasound irradiation to activate localised growth and retention of dispersed gas microbubbles as described at page 4 lines 24 *et seq.* of the specification. A particularly important advantage is that described at page 32 lines 25 *et seq.*, viz. that the dispersed gas will be temporarily retained in concentrations proportional to the regional rate of tissue perfusion. Accordingly, when using ultrasound imaging modalities such as normal or harmonic B-mode imaging where the display derives directly from return signal intensities, images of such tissue will constitute perfusion maps in which the signal intensity at any point is a direct representation of the rate of tissue perfusion at that point.

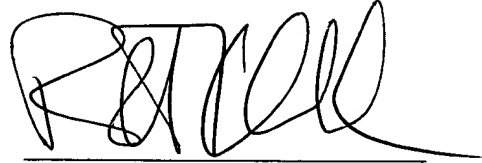
A second key feature of the instant invention is the use of surface materials with opposite charges in compositions (i) and (ii) respectively. This feature and the advantages which accrue therefrom have been discussed earlier in context of the nonstatutory double patenting rejection.

Applicants respectively submit that neither of these key features, nor the advantages arising therefrom, can in any way be deduced from Unger and Lohrmann either separately or in combination. Both of these disclosures are simply concerned with gas-containing or gas-generating ultrasound contrast agents, respectively. The skilled reader will have no motivation to combine these products and would not be able to predict from such a combination the highly advantageous properties of the presently claimed combined preparations, since there is no suggestion in the art that dispersed gas and oil phases might interact in the manner found by the applicant and defined in the instant claims. Therefore, as neither Unger nor Lohrmann, taken either alone or in combination, disclose, teach, or suggest a combined preparation as claimed by the present invention, Applicants respectfully submit that the present invention is patentably distinct thereover. Reconsideration and withdrawal of the rejections are respectfully requested.

In view of the amendments and remarks hereinabove, Applicants respectfully submit that the instant application, including claims 1-17, are in condition for allowance. Favorable action thereon is respectfully requested.

Any questions with respect to the foregoing may be directed to Applicants' undersigned counsel at the telephone number listed below.

Respectfully submitted,



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Melissa Leck
Signature [Handwritten Signature]
Date January 29 2003



Specification (marked up version showing amendments)

Please amend the paragraph at page 56, lines 13-15 as follows in order to correct a typographical error changing "nd" to "and":

- a) [Comparative] Imaging using negatively charged perfluorobutane gas dispersion
[nd]and negatively charged perfluorodimethylcyobutane emulsion